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I, the undersigned, being an officer duly authorised in accordance with Section 74(1) and (4) of the Deregulation & Contracting Out Act 1994, to sign and issue certificates on behalf of the Comptroller-General, hereby certify that annexed hereto is a true copy of the documents as originally filed in connection with the patent application identified therein.

In accordance with the Patents (Companies Re-registration) Rules 1982, if a company named in this certificate and any accompanying documents has re-registered under the Companies Act 1980 with the same name as that with which it was registered immediately before re-registration save for the substitution as, or inclusion as, the last part of the name of the words "public limited company" or their equivalents in Welsh, references to the name of the company in this certificate and any accompanying documents shall be treated as references to the name with which it is so re-registered.

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Dated 4 December 2006

Patents Form 1/77

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1/77

THE PATENT OFFICE J 26 JAN 2002 NEWPORT

THE PATENT OFFICE E 28 JAN 2002 NEWPORT

Request for grant of a patent

(See the notes on the back of this form. You can also get an explanatory leaflet from the Patent Office to help you fill in this form)

The Patent Office

Concept House
Cardiff Road
Newport
South Wales
NP10 8QQ

1. Your reference — PHAZ / P25718GB

2. Patent application number *(The Patent Office will fill in this part)* — **0201794.5**

28JAN02 E691100 3 002066
P01/7700 0.00-0201794.5

26 JAN 2002

3. Full name, address and postcode of the or of each applicant *(underline all surnames)*

Pharmacore AB
c/o A+ Science Invest AB
P.O. Box 3096
SE-400 10 Göteborg
Sweden

Patents ADP number *(if you know it)* 8157158002

If the applicant is a corporate body, give the country/state of its incorporation — Sweden

4. Title of the invention

PHARMACEUTICALLY-USEFUL COMPOUNDS

5. Name of your agent *(if you have one)*

"Address for service" in the United Kingdom to which all correspondence should be sent *(including the postcode)*

ERIC POTTER CLARKSON
PARK VIEW HOUSE
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NOTTINGHAM
NG1 5DD

Patents ADP number *(if you know it)* **1305010**

6. If you are declaring priority from one or more earlier patent applications, give the country and the date of filing of the or of each of these earlier applications and *(if you know it)* the or each application number

Country	Priority application number *(if you know it)*	Date of filing *(day / month / year)*

7. If this application is divided or otherwise derived from an earlier UK application, give the number and the filing date of the earlier application

Number of earlier application	Date of filing *(day / month / year)*

8. Is a statement of inventorship and of right to grant of a patent required in support of this request? *(Answer 'Yes' if:*

a) *any applicant named in part 3 is not an inventor; or*
b) *there is an inventor who is not named as an applicant, or*
c) *any named applicant is a corporate body. See note (d))*

YES

Patents Form 1/77

9. Enter the number of sheets for any of the following items you are filing with this form. Do not count copies of the same document

Continuation sheets of this form	
Description	45
Claims*(s)*	10
Abstract	1
Drawing*(s)*	0

10. If you are also filing in any of the following, state how many against each item.

Priority Documents	0
Translations of priority documents	0
Statement of inventorship and right to grant of a patent *(Patents Form 7/77)*	YES
Request for preliminary examination and search *(Patents Form 9/77)*	NO
Request for substantive examination *(Patents Form 10/77)*	NO
Any other documents *(please specify)*	

11. I/We request the grant of a patent on the basis of this application.

Signature **ERIC POTTER CLARKSON** Date 25 January 2002

12. Name and daytime telephone number of person to contact in the United Kingdom **0115 9552211**

Warning

After an application for a patent has been filed, the Comptroller of the Patent Office will consider whether publication or communication of the invention should be prohibited or restricted under Section 22 of the Patents Act 1977. You will be informed if it is necessary to prohibit or restrict your invention in this way. Furthermore, if you live in the United Kingdom, Section 23 of the Patents Act 1977 stops you from applying for a patent abroad without first getting written permission from the Patent Office unless an application has been filed at least 6 weeks beforehand in the United Kingdom for a patent for the same invention and either no direction prohibiting publication or communication has been given, or any such direction has been revoked.

Notes

a) If you need help to fill in this form or you have any questions, please contact the Patent Office on 01645 500505.
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d) If you have answered 'Yes' Patents Form 7/77 will need to be filed.
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Statement of inventorship and of right to grant of a patent

1.	Your reference	PHAZ / P25718GB
2.	Patent application number *(if you know it)*	0201794.5 — 26 JAN 2002
3.	Full name of the or of each applicant	Pharmacore AB
4.	Title of the invention	PHARMACEUTICALLY-USEFUL COMPOUNDS
5.	State how the applicant*(s)* derived the right from the inventor*(s)* to be granted a patent	By Assignment
6.	How many, if any, additional Patents Forms 7/77 are attached to this form? *(see note (c))*	
7.		I/We believe that the person*(s)* named over the *page (and on any extra copies of this form)* is/are the inventor*(s)* of the invention which the above patent application relates to.
		Signature Date
		ERIC POTTER CLARKSON 25 January 2002
8.	Name and daytime telephone number of person to contact in the United Kingdom	**0115 9552211**

Notes

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b) Write your answers in capital letters using black ink or you may type them.
c) If there are more than three inventors, please write the names and addresses of the other inventors on the back of another Patents Form 7/77 and attach it to this form.
d) When an application does not declare any priority, or declares priority from an earlier UK application, you must provide enough copies of this form so that the Patent Office can send one to each inventor who is not an applicant.
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Enter the full names, addresses and postcodes of the inventors in the boxes and underline the surnames

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Patents ADP number *(if you know it)*: 8[illegible]

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Patents ADP number *(if you know it)*:

Reminder

Have you signed this form?

PHARMACEUTICALLY-USEFUL COMPOUNDS

Field of the Invention

This invention relates to novel pharmaceutically-useful compounds, in particular compounds that are angiotensin II (AngII) agonists, more particularly agonists of the AngII type 2 receptor (hereinafter the AT2 receptor), and especially agonists that bind selectively to that receptor. The invention further relates to the use of such compounds as medicaments, to pharmaceutical compositions containing them, and to synthetic routes to their production.

Background and Prior Art

The endogenous hormone AngII is a linear octapeptide (Asp^1-Arg^2-Val^3-Tyr^4-Ile^5-His^6-Pro^7-Phe^8), and is the active component of the renin-angiotensin system (RAS). It is produced by the sequential processing of the pro-hormone angiotensinogen by renin and angiotensin converting enzyme (ACE).

The renin-angiotensin system (RAS) plays an important role in the regulation of blood pressure, body fluid and electrolyte homeostasis. Ang II exerts these physiological actions in many organs including the kidneys, the adrenal glands, the heart, blood vessels, the brain, the gastrointestinal tract and the reproductive organs (de Gasparo *et al*, *Pharmacol. Rev.* (2000) **52**, 415-472).

Two main classes of AngII receptors have been identified, and designated as the type 1 receptor (hereinafter the AT1 receptor) and the AT2 receptor. The AT1 receptor is expressed in most organs, and is believed to be

responsible for the majority of the biological effects of AngII. The AT2 receptor is more prevalent than the AT1 receptor in fetal tissues, the adult ovaries, the adrenal medulla and the pancreas. An equal distribution is reported in the brain and uterus (Ardaillou, *J. Am. Soc. Nephrol.*, **10**, S30-39 (1999)).

Several studies in adult individuals appear to demonstrate that, in the modulation of the response following AngII stimulation, activation of the AT2 receptor has opposing effects to those mediated by the AT1 receptor.

The AT2 receptor has also been shown to be involved in apoptosis and inhibition of cell proliferation (see de Gasparo *et al, supra*). Further, it seems to play a role in blood pressure control. For example, it has been shown in transgenic mice lacking AT2 receptors that their blood pressure was elevated. Furthermore, it has been concluded that the AT2 receptor is involved in exploratory behaviour, pain sensitivity and thermoregulation.

The expression of AT2 receptors has also been shown to increase during pathological circumstances, such as vascular injury, wound healing and heart failure (see de Gasparo *et al, supra*).

The expected pharmacological effects of agonism of the AT2 receptor are described generally in de Gasparo *et al, supra*.

More recently, AT2 receptor agonists have been shown to be of potential utility in the treatment and/or prophylaxis of disorders of the alimentary tract, such as dyspepsia and irritable bowel syndrome, as well as multiple organ failure (see international patent application WO 99/43339).

AngII antagonists (which bind to the AT1 and/or AT2 receptors) have been disclosed in *inter alia* European patent application EP 512 675; international patent applications WO 94/27597, WO 94/02142, WO 95/23792 and WO 94/03435; and US patent numbers 5,091,390, 5,177,074, 5,412,097, 5,444,067, 5,520,521, 5,260,285, 5,376,666, 5,252,574, 5,312,820, 5,330,987, 5,166,206, 5,932,575 and 5,240,928. AngII agonists, and particularly AT2 receptor agonists, are not contemplated in any of these documents.

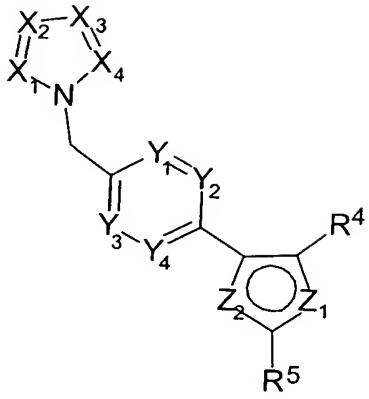
International patent application WO 00/68226 and US patent number 6,235,766 disclose compounds comprising substituted imidazolyl groups, which groups are attached, *via* a methylene bridge, to a phenylthiophene moiety, as agonists of angiotensin-(1-7) receptors. The use of the compounds as Ang II receptor agonists is neither mentioned nor suggested.

Peptide and non-peptide AT2 receptor agonists, unrelated structurally to those described herein, and potential uses thereof, have been disclosed in, for example, international patent applications WO 00/38676, WO 00/56345, WO 00/09144, WO 99/58140, WO 99/52540, WO 99/46285, WO 99/45945, WO 99/42122, WO 99/40107, WO 99/40106, WO 99/39743, WO 99/26644, WO 98/33813, WO 00/02905 and WO 99/46285; US patent number 5,834,432; and Japanese patent application JP 143695.

However, there remains a need for effective and/or selective AT2 receptor agonists, which are expected to find utility in *inter alia* the above-mentioned conditions.

Disclosure of the Invention

According to the invention there is provided a compound of formula I,



I

wherein

one of X_1 and X_2 represents –N- and the other represents $-C(R^1)-$;

X_3 represents –N- or $-C(R^2)-$;

X_4 represents –N- or $-C(R^3)-$;

R^1, R^2 and R^3 independently represent H, C_{1-6} alkyl, C_{1-6} alkoxy, C_{1-6} alkoxy-C_{1-6}-alkyl or halo;

provided that, when X_1 represents $-C(R^1)-$, X_3 represents $-C(R^2)-$ and X_4 represents $-C(R^3)-$, then R^1 represents H;

Y_1, Y_2, Y_3 and Y_4 independently represent –CH- or -CF-;

Z_1 represents –CH-, -O-, -S-, -N- or -CH=CH-;

Z_2 represents –CH-, -O-, -S- or –N-;

provided that:

(a) Z_1 and Z_2 are not the same;

(b) when Z_1 represents –CH=CH-, then Z_2 may only represent –CH- or –N-; and

(c) other than in the specific case in which Z_1 represents –CH=CH-, and Z_2 represents –CH-, when one Z_1 and Z_2 represents –CH-, then the other represents –O- or –S-;

R^4 represents $-S(O)_2N(H)C(O)R^6$, $-S(O)_2N(H)S(O)_2R^6$, $-C(O)N(H)S(O)_2R^6$, or, when Z_1 represents –CH=CH-, R^4 may represent $-N(H)S(O)_2N(H)C(O)R^7$ or $-N(H)C(O)N(H)S(O)_2R^7$;

R^5 represents C_{1-6} alkyl, C_{1-6} alkoxy or C_{1-6} alkoxy-C_{1-6}-alkyl;

R^6 represents C_{1-6} alkyl, C_{1-6} alkoxy, C_{1-6} alkoxy-C_{1-6}-alkyl, C_{1-6} alkylamino or di-C_{1-6} alkylamino; and

R^7 represents C_{1-6} alkyl,

or a pharmaceutically-acceptable salt thereof,

provided that, when X_1, X_3 and X_4 all represent –CH-, Y_1, Y_2, Y_3 and Y_4 all represent –CH-, Z_1 represents –S- or –CH=CH-, Z_2 represents –CH- and R^5 represents *n*-butyl or *iso*-butyl, then R^4 does not represent $-S(O)_2N(H)C(O)R^6$, in which R^6 represents -O-*n*-butyl, -O-*iso*-propyl, -O-*iso*-butyl or $-CH_2$-O-*n*-butyl,

which compounds and salts are referred to together hereinafter as "the compounds of the invention".

Pharmaceutically-acceptable salts include acid addition salts and base addition salts. Such salts may be formed by conventional means, for example by reaction of a free acid or a free base form of a compound of the invention with one or more equivalents of an appropriate acid or base, optionally in a solvent, or in a medium in which the salt is insoluble, followed by removal of said solvent, or said medium, using standard techniques (e.g. *in vacuo* or by freeze-drying). Salts may also be prepared by exchanging a counter-ion of a compound of the invention in the form of a salt with another counter-ion, for example using a suitable ion exchange resin.

Unless otherwise specified, alkyl groups, and the alkyl parts of alkoxy, alkoxyalkyl and alkylamino groups, as defined herein may be straight-chain or, when there is a sufficient number (i.e. a minimum of three) of carbon

atoms, be branched-chain, and/or cyclic. Further, when there is a sufficient number (i.e. a minimum of four) of carbon atoms, such groups may also be part cyclic/acyclic. Such alkyl groups, and alkyl parts of alkoxy, alkoxyalkyl and alkylamino groups, may also be saturated or, when there is a sufficient number (i.e. a minimum of two) of carbon atoms, be unsaturated. Unless otherwise specified, such groups may also be substituted by one or more halo, and especially fluoro, atoms.

For the avoidance of doubt, alkoxy groups are attached to the rest of the molecule *via* the oxygen atom in that group, alkylamino groups are attached to the rest of the molecule *via* the nitrogen atom of the amino part of that group and alkoxyalkyl groups are attached to the rest of the molecule *via* the alkyl part of that group.

The term "halo", when used herein, includes fluoro, chloro, bromo and iodo.

Preferred ring systems comprising the substituents Y_1, Y_2, Y_3 and Y_4 include phenyl groups. For the avoidance of doubt, the ring systems in compounds of formula I that comprise the groups Z_1 and Z_2, are aromatic in nature. In some instances, for example in cases where one or more of Z_1 and Z_2 represent –CH- or –N- the skilled person will appreciate that an additional H atom may necessarily be bonded to that CH group or N atom, in order to ensure that the rules of valency are adhered to. Preferred ring systems comprising Z_1 and Z_2 include oxazole groups, thiazole groups, phenyl groups, pyridinyl groups, thiophenyl groups and furanyl groups.

In this respect, compounds of the invention may exhibit tautomerism. All tautomeric forms and mixtures thereof are included within the scope of the invention.

Compounds of the invention also contain one or more asymmetric carbon atoms and may therefore exhibit optical and/or diastereoisomerism. Diastereoisomers may be separated using conventional techniques, e.g. chromatography or fractional crystallisation. The various stereoisomers may be isolated by separation of a racemic or other mixture of the compounds using conventional, e.g. fractional crystallisation or HPLC, techniques. Alternatively the desired optical isomers may be made by reaction of the appropriate optically active starting materials under conditions which will not cause racemisation or epimerisation, or by derivatisation, for example with a homochiral acid followed by separation of the diastereomeric derivatives by conventional means (e.g. HPLC, chromatography over silica). All stereoisomers are included within the scope of the invention.

Preferred compounds of the invention include those in which:

(i) when X_1 represents $-C(R^1)-$, then:

(a) X_3 represents $-C(R^2)-$ and X_4 represents $-N-$;

(b) X_3 and X_4 both represent N; or

(c) X_3 represents $-C(R^2)-$ and X_4 represents $-C(R^3)-$; or

(ii) when X_1 represents $-N-$, then X_3 represents $-N-$.

In case (i)(a) above, it is further preferred that R^1 represents H.

In case (ii) above, when X_4 represents $-C(R^3)-$, it is further preferred that R^3 represents H.

Preferred compounds of formula I include those in which:

R^1 represents C_{1-3} alkyl, such as ethyl, or, especially, H;

R^2 represents C_{1-3} alkyl, halo or, especially, H;

R^3 represents C_{1-3} alkyl, halo or, especially, H;

Y_1, Y_2, Y_3 and Y_4 all represent –CH-;

Z_1 represents -S- or –CH=CH-;

Z_2 represents –CH-;

R^4 represents $S(O)_2N(H)C(O)R^6$;

R^5 represents *n*-butyl or, particularly, *iso*-butyl;

R^6 represents *n*-butoxymethyl, *iso*-butoxy and especially, *n*-butoxy.

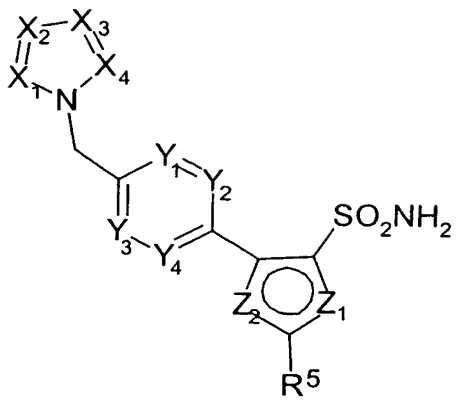
Preferred ring systems comprising the substituents X_1, X_2, X_3 and X_4 include imidazole groups, 1,2,4-triazole groups and tetrazole groups.

More preferred compounds of the invention include the compounds of the examples described hereinafter.

Compounds of formula I may be made in accordance with techniques well known to those skilled in the art, for example as described hereinafter.

According to a further aspect of the invention there is provided a process for the preparation of a compound of formula I, which process comprises:

(i) for compounds of formula I in which R^4 represents $-S(O)_2N(H)C(O)R^6$ or $-S(O)_2N(H)S(O)_2R^6$, and R^6 is as hereinbefore defined, reaction of a compound of formula II,



II

wherein X_1, X_2, X_3, X_4, Y_1, Y_2, Y_3, Y_4, Z_1, Z_2 and R^5 are as hereinbefore defined with a compound of formula III,

$$R^6GL^1 \qquad \text{III}$$

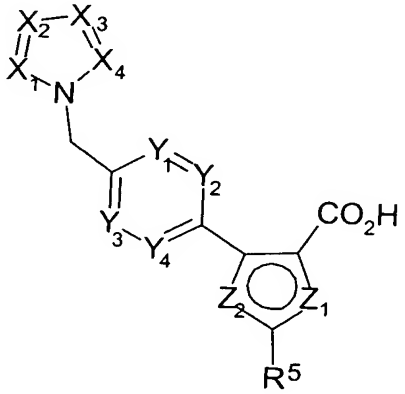
wherein G represents C(O) or $S(O)_2$ (as appropriate), L^1 represents a suitable leaving group, such as halo (e.g. chloro or bromo) and R^6 is as hereinbefore defined, for example at around room temperature or above (e.g. up to 60-70°C) in the presence of a suitable base (e.g. pyrollidinopyridine, pyridine, triethylamine, tributylamine, trimethylamine, di-*iso*-propylamine, 1,8-diazabicyclo[5.4.0]undec-7-ene, sodium hydroxide, or mixtures thereof) and an appropriate solvent (e.g. pyridine, dichloromethane, chloroform, tetrahydrofuran, dimethylformamide, trifluoromethylbenzene or triethylamine). Preferred base/solvent systems for compounds of formula III in which G is C(O) include pyrollidinopyridine/pyridine. Preferred base/solvent systems for compounds of formula III in which G is $S(O)_2$ include NaOH/THF;

(ii) for compounds of formula I in which R^4 represents $-S(O)_2N(H)C(O)R^6$ and R^6 represents C_{1-6} alkoxy-C_{1-6}-alkyl, coupling of a compound of formula II as hereinbefore defined with a compound of formula IV,

$R^{6a}CO_2H$ IV

wherein R^{6a} represents C_{1-6} alkoxy-C_{1-6}-alkyl, for example under similar conditions to those described under process step (i) above, in the presence of a suitable coupling reagent (e.g. 1,1'-carbonyl-diimidazole, N,N'-dicyclohexylcarbodiimide, N,N'-disuccinimidyl carbonate, benzotriazole-1-yloxytris(dimethylamino)phosphoniumhexafluorophosphate, 2-(1H-benzotriazole-1-yl)-1,1,3,3-tetramethyluronium hexafluorophosphate, benzotriazole-1-yl-oxy-tris-pyrrolidino-phosphonium hexafluorophosphate, bromo-tris-pyrrolidinophosponium hexafluorophosphate or 2-(1H-benzotriazole-1-yl)-1,1,3,3-tetramethyluronium tetrafluorocarbonate), a suitable base (as mentioned in process step (i) above) and an appropriate solvent (as mentioned in process step (i) above);

(iii) for compounds of formula I in which R^4 represents $-C(O)N(H)S(O)_2R^6$ and R^6 is as hereinbefore defined, coupling of a compound of formula V,



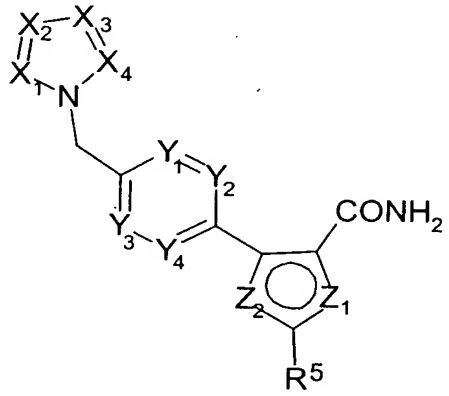
V

wherein X_1, X_2, X_3, X_4, Y_1, Y_2, Y_3, Y_4, Z_1, Z_2 and R^5 are as hereinbefore defined with a compound of formula VI,

$R^6S(O)_2NH_2$ VI

wherein R^6 is as hereinbefore defined, for example in the presence of a suitable coupling reagent (such as those described in process step (ii) hereinbefore), and under similar reaction conditions to those described hereinbefore for preparation of compounds of formula I in which R^6 represents C_{1-6} alkoxy-C_{1-6}-alkyl;

(iv) for compounds of formula I in which R^4 represents $-C(O)N(H)S(O)_2R^6$ and R^6 is as hereinbefore defined, coupling of a compound of formula VA,



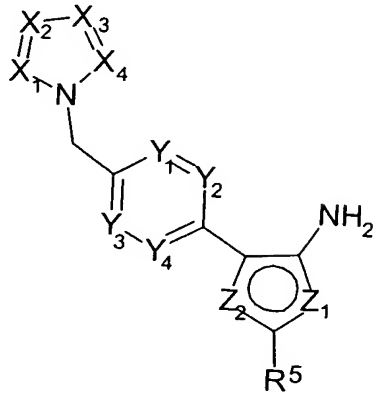
VA

wherein X_1, X_2, X_3, X_4, Y_1, Y_2, Y_3, Y_4, Z_1, Z_2 and R^5 are as hereinbefore defined with a compound of formula VIA,

$R^6S(O)_2Cl$ VIA

wherein R^6 is as hereinbefore defined, for example at around 50°C in the presence of a suitable base (e.g. sodium hydride) and an appropriate organic solvent (e.g. THF);

(v) for compounds of formula I in which R^4 represents $-N(H)S(O)_2N(H)C(O)R^7$ and R^7 is as hereinbefore defined, reaction of a compound of formula VII,



VII

wherein X_1, X_2, X_3, X_4, Y_1, Y_2, Y_3, Y_4, Z_1, Z_2 and R^5 are as hereinbefore defined with a compound of formula VIII,

$$R^7C(O)N(H)S(O)_2Cl \qquad \text{VIII}$$

wherein R^7 is as hereinbefore defined, for example at or around room temperature in the presence of a suitable base (e.g. sodium hydroxide or triethylamine) and a suitable organic solvent (e.g. benzene or dichloromethane);

(vi) for compounds of formula I in which R^4 represents $-N(H)C(O)N(H)S(O)_2R^7$ and R^7 is as hereinbefore defined, reaction of a compound of formula VII as hereinbefore defined with a compound of formula IX,

$$R^7S(O)_2N(H)C(O)OR^x \qquad \text{IX}$$

wherein R^x represents C_{1-2} alkyl and R^7 is as hereinbefore defined, for example at or around room temperature in the presence of a suitable organic solvent (e.g. dichloromethane);

(vii) for compounds of formula I in which R^4 represents $-N(H)C(O)N(H)S(O)_2R^7$ and R^7 is as hereinbefore defined, reaction of a compound of formula VII as hereinbefore defined with an isocyanate compound of formula X,

$$R^7S(O)_2NCO \qquad X$$

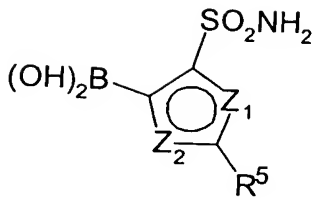
wherein R^7 is as hereinbefore defined, for example at or around room temperature in the presence of a suitable organic solvent (e.g. dichloromethane); or

(viii) for compounds of formula I in which R^4 represents $-S(O)_2N(H)C(O)R^6$ and R^6 represents C_{1-6} alkylamino, reaction of a compound of formula II as hereinbefore defined with an isocyanate compound of formula XA,

$$R^{6a}NCO \qquad XA$$

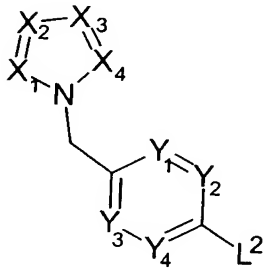
wherein R^{6a} is C_{1-6} alkyl, for example at or around room temperature in the presence of a suitable base (e.g. sodium hydroxide or potassium hydroxide and an appropriate organic solvent (e.g. acetone or acetonitrile).

Compounds of formula II may be prepared by reaction of a compound of formula XI,



XI

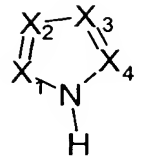
wherein R^5, Z^1 and Z^2 are as hereinbefore defined, or a N-protected derivative thereof, with a compound of formula XII,



XII

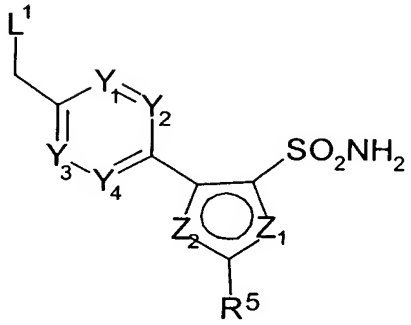
wherein L^2 represents a suitable leaving group, such as trimethylsulphonate, or halo, such as iodo or bromo, and X_1, X_2, X_3, X_4, Y_1, Y_2, Y_3 and Y_4 are as hereinbefore defined, for example in the presence of an appropriate coupling catalyst system (e.g. a palladium catalyst, such as $Pd(PPh_3)_4$ or $Pd(OAc)_2$ and a suitable base (e.g. sodium hydroxide, sodium carbonate, cesium carbonate, triethylamine or di-*iso*-propylamine)), as well as a suitable solvent system (e.g. toluene, ethanol, dimethoxymethane, dimethylformamide, water, dioxane or mixtures thereof). This reaction may be carried out at above room temperature (e.g. at the reflux temperature of the solvent system that is employed). If a protected version of a compound of formula XI is employed, this reaction may be followed by deprotection of the SO_2NH-group under standard conditions, for example as described hereinafter.

Compounds of formula II may alternatively be prepared by reaction of a compound of formula XIII,



XIII

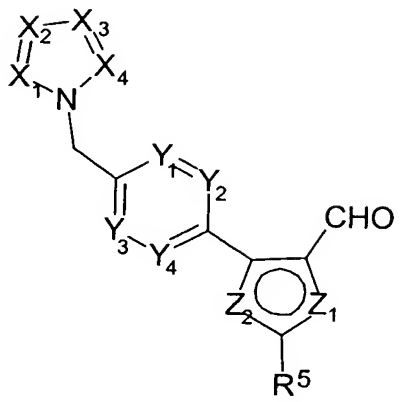
wherein X_1, X_2, X_3 and X_4 are as hereinbefore defined with a compound of formula XIV,



XIV

wherein Y_1, Y_2, Y_3, Y_4, Z_1, Z_2, R^5 and L^1 are as hereinbefore defined (L^1, in particular, may represent bromo), or a N-protected derivative thereof, for example at around or below room temperature in the presence of a suitable base (e.g. potassium hydroxide) and an appropriate organic solvent (e.g. DMSO). If a protected version of a compound of formula XIV is employed, this reaction may be followed by deprotection of the SO_2NH- group under standard conditions, for example as described hereinafter. Additionally, compounds of formula II in which Z_1 is –CH=CH- and Z_2 is –CH- may be prepared in this way, for example according, or analogously, to processes described in *inter alia* US patent number 5,312,820. Further, compounds of formula II in which Z_1 is –S- and Z_2 is –CH- may be prepared in this way for example according, or analogously, to processes described in *inter alia* UK patent application GB 2281298.

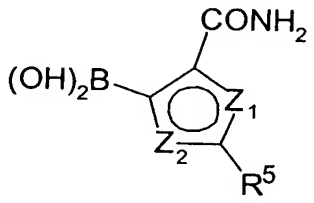
Compounds of formula V may be prepared by oxidation of a compound of formula XV,



XV

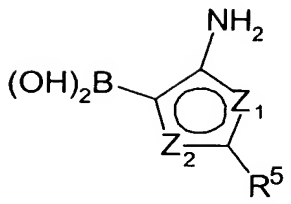
wherein X_1, X_2, X_3, X_4, Y_1, Y_2, Y_3, Y_4, Z_1, Z_2 and R^5 are as hereinbefore defined, for example under standard oxidation conditions in the presence of a suitable oxidising agent, such as potassium permanganate or chromium (VI) oxide.

Compounds of formula VA and VII may be prepared by reaction of a compound of formula XII as hereinbefore defined with (in the case of a compound of formula VA) a compound of formula XVA,



XVA

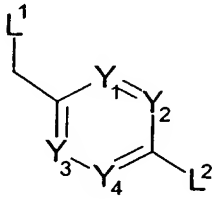
or (in the case of a compound of formula VII) a compound of formula XVI,



XVI

wherein, in both cases, Z_1, Z_2 and R^5 are as hereinbefore defined, or N-protected derivatives thereof, for example under similar conditions to those described hereinbefore for preparation of compounds of formula II (first process). If protected versions of compounds of formulae XVA and XVI are employed, these reactions may be followed by deprotection of the NH-group under standard conditions (e.g. acid hydrolysis).

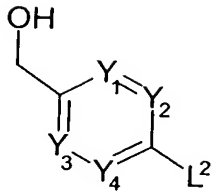
Compounds of formula XII may be prepared by standard techniques, for example by way of reaction of a compound of formula XIII as hereinbefore defined with a compound of formula XVII,



XVII

wherein Y_1, Y_2, Y_3, Y_4, L^1 and L^2 are as hereinbefore defined, for example under similar conditions to those described hereinbefore in respect of preparation of compounds of formula II (second process).

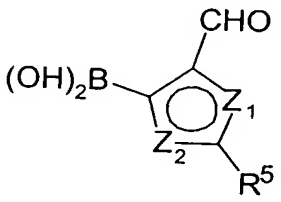
Compounds of formula XIV are known in the art. For example, they may be prepared according, or analogously, to processes described in *inter alia* US patent number 5,312,820, UK patent application GB 2281298, and/or by reaction of a compound of formula XI as hereinbefore defined with a compound of formula XVIII,



XVIII

wherein Y_1, Y_2, Y_3, Y_4 and L^2 are as hereinbefore defined, for example under similar conditions to those described hereinbefore in respect of preparation of compounds of formula II (first process), followed by conversion of the OH group in the resultant intermediate to an appropriate leaving group, L^1 (e.g., in the case where L^1 is bromo, conversion may be carried out by reaction with CBr_4, for example at or around room temperature in the presence of a base (e.g. triphenylphosphine) and a suitable organic solvent (e.g. DMF)).

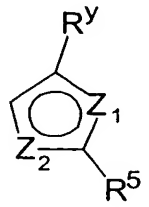
Compounds of formula XV may be prepared by reaction of a compound of formula XII as hereinbefore defined with a compound of formula XIX,



XIX

wherein Z_1, Z_2 and R^5 are as hereinbefore defined, or a protected (at the aldehyde part) derivative thereof, for example under similar conditions to those described hereinbefore for preparation of compounds of formula II (first process). If a protected version of a compound of formula XIX is employed, this reaction may be followed by deprotection of the CHO-group under standard conditions (e.g. acid hydrolysis).

Compounds of formulae XI, XVA, XVI and XIX and protected derivatives thereof may be prepared by reaction of a corresponding compound of formula XX,

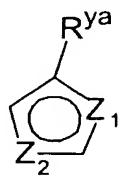


XX

wherein R^y represents $-S(O)_2NH_2$, $-C(O)NH_2$, $-NH_2$ or $-CHO$ (as appropriate) and R^5, Z_1 and Z_2 are as hereinbefore defined, or an appropriate protected derivative thereof, with a reagent system that will enable the introduction of the $-B(OH)_2$ into the appropriate ring system. Suitable reagent systems include trialkylborates (e.g. tri-*iso*-propylborate). Such reactions may be carried out, for example, at low temperature (e.g. between -100°C and 0°C, e.g. between -80°C (such as -78°C) and –10°C (such as -20°C)) in the presence of a suitable base (e.g. *n*-butyl lithium) and an appropriate organic solvent (e.g. THF), followed by acid hydrolysis (e.g. in the presence of dilute HCl).

Compounds of formula XX are available using known techniques. For example:

(a) Compounds of formula XX in which R^y represents $-S(O)_2NH_2$, $-C(O)NH_2$ or –CHO, and protected derivatives thereof, may be prepared by reaction of a compound of formula XXI,



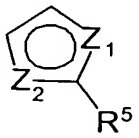
XXI

wherein R^{ya} represents $-S(O)_2NH_2$, $-C(O)NH_2$ or $-CHO$ and Z_1 and Z_2 are as hereinbefore defined, or a protected derivative thereof, with a compound of formula XXII,

$$R^5L^3 \qquad \text{XXII}$$

wherein L^3 represents a suitable leaving group (such as toluenesulphonate, benzenesulphonate, methanesulphonate or halo, such as bromo or iodo) and R^5 is as hereinbefore defined, for example at below room temperature (e.g. between around -35°C and around -85°C), in the presence of a suitable base (e.g. *n*-butyl lithium) and an appropriate solvent (e.g. THF).

(b) Compounds of formula XX in which R^y is $-S(O)_2NH_2$ and N-protected derivatives thereof, may be prepared by reaction of an appropriate compound of formula XXIII,



XXIII

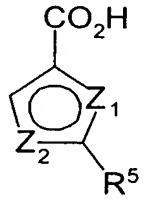
wherein R^5, Z_1 and Z_2 are as hereinbefore defined with an appropriate reagent for introduction of a $-S(O)_2NH_2$ group into the appropriate ring system (for example chlorosulphonic acid, or thionyl chloride in the presence of a suitable strong base (e.g. butyl lithium)), followed by reaction of the resultant intermediate with ammonia, or a protected derivative thereof (e.g. *tert*-butylamine), under conditions that are well known to those skilled in the art.

(c) Certain protected derivatives (e.g. alkyl, such as C_{1-6} alkyl, for example *tert*-butyl, protected derivatives) of compounds of formula XX in which R^y represents $-C(O)NH_2$ may be prepared by reaction of a compound of formula XXIII as hereinbefore defined, with a compound of formula XXIV,

$$R^ZN=C=O \qquad \text{XXIV}$$

wherein R^Z represents an appropriate protecting group, such as an alkyl group, including C_{1-6} alkyl, e.g. *tert*-butyl, for example at around 0°C, in the presence of a suitable base (e.g. *n*-butyl lithium) and an appropriate solvent (e.g. THF).

(d) Certain protected derivatives (e.g. alkyl, such as C_{1-6} alkyl, for example *tert*-butyl, protected derivatives) of compounds of formula XX in which R^y represents $-C(O)NH_2$ may also be prepared by reaction of a compound of formula XXV,



XXV

wherein R^5, Z_1 and Z_2 are as hereinbefore defined with a protected (e.g. an (e.g. C_{1-6}) alkyl, such as *tert*-butyl-protected) derivative of ammonia (e.g. *tert*-butylamine) under standard coupling conditions (see, for example, those described hereinbefore for preparation of compounds of formula I (process step (iii))). Compounds of formula XXV are known in the art or may be prepared by way of standard techniques, for example oxidation of a corresponding compound of

formula XX in which R^y is -CHO e.g. under those conditions described hereinbefore for preparation of compounds of formula V.

(e) Compounds of formula XX in which R^y is –CHO, Z_1 represents –CH=CH- and Z_2 represents –CH-, and protected derivatives thereof, may be prepared by reaction of a compound of formula XXIII in which Z_1 represents –CH=CH- and Z_2 represents –CH- with an appropriate reagent system for the introduction of an aldehyde group into the benzene ring (e.g. $TiCl_4/CHCl_3$, $SnCl_4/CH_2Cl_2$ or 1,3,5,7-azaadamantane/TFA) under standard reaction conditions, followed by (if appropriate) protection of the resultant benzaldehyde under standard conditions.

(f) Compounds of formula XX in which R^y is $–NH_2$, Z_1 represents –CH=CH- and Z_2 represents –CH-, and N-protected derivatives thereof, may be prepared by nitration of a compound of formula XXIII in which Z_1 represents –CH=CH- and Z_2 represents –CH-, followed by reduction of the resultant nitrobenzene and (if appropriate) protection of the resultant aminobenzene, all of which steps may be carried out under standard conditions.

Compounds of formulae III, IV, VI, VIA, VIII, IX, X, XA, XIII, XVII, XVIII, XXI, XXII, XXIII and XXIV are either commercially available, are known in the literature, or may be obtained either by analogy with the processes described herein, or by conventional synthetic procedures, in accordance with standard techniques, from readily available starting materials using appropriate reagents and reaction conditions.

Compounds of the invention may be isolated from their reaction mixtures using conventional techniques.

It will be appreciated by those skilled in the art that, in the processes described above and hereinafter, the functional groups of intermediate compounds may need to be protected by protecting groups.

Functional groups that it is desirable to protect include sulphonamido, amido, amino and aldehyde. Suitable protecting groups for sulphonamido, amido and amino include *tert*-butyloxycarbonyl, benzyloxycarbonyl, 2-trimethylsilylethoxycarbonyl (Teoc) or *tert*-butyl. Suitable protecting groups for aldehyde include alcohols, such as methanol or ethanol, and diols, such as 1,3-propanediol or, preferably, 1,2-ethanediol (so forming a cyclic acetal).

The protection and deprotection of functional groups may take place before or after a reaction in the above-mentioned schemes.

Protecting groups may be removed in accordance with techniques that are well known to those skilled in the art and as described hereinafter. For example, protected compounds/intermediates described herein may be converted chemically to unprotected compounds using standard deprotection techniques (e.g. using trifluoroacetic acid, sulfuric acid, toluenesulfonic acid or boron trichloride).

Persons skilled in the art will appreciate that, in order to obtain compounds of the invention in an alternative, and, on some occasions, more convenient, manner, the individual process steps mentioned hereinbefore may be performed in a different order, and/or the individual reactions may be performed at a different stage in the overall route (i.e. substituents may be added to and/or chemical transformations performed upon, different intermediates to those mentioned hereinbefore in conjunction with a

particular reaction). This may negate, or render necessary, the need for protecting groups.

The type of chemistry involved will dictate the need, and type, of protecting groups as well as the sequence for accomplishing the synthesis.

The use of protecting groups is fully described in "Protective Groups in Organic Chemistry", edited by J W F McOmie, Plenum Press (1973), and "Protective Groups in Organic Synthesis", 3rd edition, T.W. Greene & P.G.M. Wutz, Wiley-Interscience (1999).

Medical and Pharmaceutical Uses

Compounds of the invention are useful because they possess pharmacological activity. The compounds of the invention are therefore indicated as pharmaceuticals.

According to a further aspect of the invention there is thus provided the compounds of the invention for use as pharmaceuticals.

In particular, compounds of the invention are agonists of AngII, more particularly, are agonists of the AT2 receptor, and, especially, are selective agonists of that sub-receptor, for example as may be demonstrated in the tests described below.

The compounds of the invention are thus expected to be useful in those conditions in which endogenous production of AngII is deficient and/or where an increase in the effect of AngII is desired or required.

The compounds of the invention are further expected to be useful in those conditions where AT2 receptors are expressed and their stimulation is desired or required.

The compounds of the invention are further indicated in the treatment of conditions characterised by vasoconstriction, increased cell growth and/or differentiation, increased cardiac contractility, increased cardiovascular hypertrophy, and/or increased fluid and electrolyte retention.

The compounds of the invention are further indicated in the treatment of stress-related disorders, and/or in the improvement of microcirculation and/or mucosa-protective mechanisms.

Thus, compounds of the invention are expected to be useful in the treatment of disorders, which may be characterised as indicated above, and which are of, for example, the gastrointestinal tract, the cardiovascular system, the respiratory tract, the kidneys, the eyes, the female reproductive (ovulation) system and the central nervous system (CNS).

Disorders of the gastrointestinal tract that may be mentioned include oesophagitis, gastric ulcers, duodenal ulcers, dyspepsia (including non-ulcer dyspepsia), gastro-oesophageal reflux, irritable bowel syndrome (IBS), inflammatory bowel disease (IBD), pancreatitis, hepatitis, gall bladder disease, multiple organ failure (MOF) and sepsis. Other gastrointestinal disorders that may be mentioned include xerostomia, gastritis, gastroparesis, hyperacidity, disorders of the bilary tract, coelicia, Crohn's disease, ulcerative colitis, diarrhoea, constipation, colic, dysphagia, vomiting, nausea, indigestion and Sjögren's syndrome.

Disorders of the respiratory tract that may be mentioned include inflammatory disorders, such as asthma, obstructive lung diseases, pneumonitis, pulmonary hypertension and adult respiratory distress syndrome.

Disorders of the kidneys that may be mentioned include renal failure, nephritis and renal hypertension.

Disorders of the eyes that may be mentioned include diabetic retinopathy, premature retinopathy and retinal microvascularisation.

Disorders of the female reproductive system that may be mentioned include ovulatory dysfunction.

Cardiovascular disorders that may be mentioned include hypertension, cardiac hypertrophy, cardiac failure, artherosclerosis, arterial thrombosis, venous thrombosis, endothelial dysfunction, endothelial lesions, post-balloon dilatation stenosis, angiogenesis, diabetic complications and microvascular dysfunction.

Disorders of the CNS that may be mentioned include cognitive dysfunctions, dysfunctions of food intake (hunger/satiety) and thirst, stroke, cerebral bleeding, cerebral embolus and cerebral infarction.

Compounds of the invention may also be useful in the modulation of growth metabolism and proliferation, for example in the treatment of hypertrophic disorders, prostate hyperplasia, autoimmune disorders, psoriasis, obesity, neuronal regeneration, the healing of ulcers, inhibition of adipose tissue hyperplasia, stem cell differentiation and proliferation, cancer (e.g. in the

gastrointestinal tract, lung cancer, etc), apoptosis, tumours (generally) and hypertrophy.

The compounds of the invention are indicated both in the therapeutic and/or prophylactic treatment of the above conditions.

According to a further aspect of the present invention, there is provided a method of treatment of a condition in which endogenous production of AngII is deficient, and/or a condition where an increase in the effect of AngII is desired or required, and/or a condition where AT2 receptors are expressed and their stimulation is desired or required, which method comprises administration of a therapeutically effective amount of a compound of the invention to a person suffering from, or susceptible to, such a condition.

The compounds of the invention will normally be administered orally, intravenously, subcutaneously, buccally, rectally, dermally, nasally, tracheally, bronchially, by any other parenteral route or *via* inhalation, in a pharmaceutically acceptable dosage form.

When the condition to be treated is multiple organ failure, preferred routes of administration are parenteral (e.g. by injection). Otherwise, the preferred route of administration for compounds of the invention is oral.

The compounds of the invention may be administered alone, but are preferably administered by way of known pharmaceutical formulations, including tablets, capsules or elixirs for oral administration, suppositories for rectal administration, sterile solutions or suspensions for parenteral or intramuscular administration, and the like.

Such formulations may be prepared in accordance with standard and/or accepted pharmaceutical practice.

According to a further aspect of the invention there is thus provided a pharmaceutical formulation including a compound of the invention, in admixture with a pharmaceutically acceptable adjuvant, diluent or carrier.

Compounds of the invention may also be administered in combination with other AT2 agonists that are known in the art, as well as in combination with AT1 receptor antagonists that are known in the art, such as losartan.

According to a further aspect of the invention, there is provided a combination product comprising:

(A) a compound of the invention; and

(B) an AT1 receptor antagonist,

wherein each of components (A) and (B) is formulated in admixture with a pharmaceutically-acceptable adjuvant, diluent or carrier.

Such combination products provide for the administration of compound of the invention in conjunction with AT1 receptor antagonist, and may thus be presented either as separate formulations, wherein at least one of those formulations comprises compound of the invention and at least one comprises AT1 receptor antagonist, or may be presented (i.e. formulated) as a combined preparation (i.e. presented as a single formulation including compound of the invention and AT1 receptor antagonist).

Thus, there is further provided:

(1) a pharmaceutical formulation including a compound of the invention and an AT1 receptor antagonist, in admixture with a pharmaceutically-acceptable adjuvant, diluent or carrier; and

(2) a kit of parts comprising components:

(a) a pharmaceutical formulation including a compound of the invention, in admixture with a pharmaceutically-acceptable adjuvant, diluent or carrier; and

(b) a pharmaceutical formulation including an AT1 receptor antagonist, in admixture with a pharmaceutically-acceptable adjuvant, diluent or carrier,

which components (a) and (b) are each provided in a form that is suitable for administration in conjunction with the other.

Depending upon the disorder and patient to be treated and the route of administration, the compounds of the invention may be administered at varying doses.

Although doses will vary from patient to patient, suitable daily doses are in the range of about 1 to 1000 mg per patient, administered in single or multiple doses. More preferred daily doses are in the range 2.5 to 250 mg per patient.

Individual doses of compounds of the invention may be in the range 1 to 100 mg.

In any event, the physician, or the skilled person, will be able to determine the actual dosage which will be most suitable for an individual patient, which is likely to vary with the condition that is to be treated, as well as the age, weight, sex and response of the particular patient to be treated. The

above-mentioned dosages are exemplary of the average case; there can, of course, be individual instances where higher or lower dosage ranges are merited, and such are within the scope of this invention.

Compounds of the invention have the advantage that they bind selectively to, and exhibit agonist activity at, the AT2 receptor. By compounds which "bind selectively" to the AT2 receptor, we include that the affinity ratio for the relevant compound (AT2:AT1) is at least 5:1, preferably at least 10:1 and more preferably at least 20:1.

The compounds of the invention may also have the advantage that they may be more efficacious than, be less toxic than, be longer acting than, be more potent than, produce fewer side effects than, be more easily absorbed than, and/or have a better pharmacokinetic profile (e.g. higher oral bioavailability and/or lower clearance) than, and/or have other useful pharmacological, physical, or chemical properties over, compounds known in the prior art.

Biological Tests

The following test procedures may be employed.

Test A

Receptor Binding Assay using Rat Liver Membrane AT_1 Receptor

Rat liver membranes were prepared according to the method of Dudley *et al* (*Mol. Pharmacol.* (1990) **38**, 370). Binding of [^{125}I]Ang II to membranes was conducted in a final volume of 0.5 mL containing 50 mM Tris-HCl (pH 7.4), 100 mM NaCl, 10 mM $MgCl_2$, 1 mM EDTA, 0.025% bacitracin, 0.2% BSA (bovine serum albumin), liver homogenate corresponding to 5 mg of the original tissue weight, [^{125}I]Ang II (70 000 cpm, 0.03 nM) and variable concentrations of test substance. Samples were incubated at 25°C for 1 h, and binding was terminated by filtration through Whatman GF/B glass-fiber

filter sheets using a Brandel cell harvester. The filters were washed with 4 × 2 mL of Tris-HCl (pH 7.4) and transferred to tubes. The radioactivity was measured in a gamma counter. The characteristics of the Ang II binding AT_1 receptor were determined by using six different concentrations (0.03-5 nmol/L) of the labeled [^{125}I]AngII. Non-specific binding was determined in the presence of 1 μM Ang II. The specific binding was determined by subtracting the non-specific binding from the total bound [^{125}I]AngII. The dissociation constant (K_d = 1.7 ± 0.1 nM, [L] = 0.057 nM) was determined by Scatchard analysis of data obtained with Ang II by using GraFit (Erithacus Software, UK). The binding data were best fitted with a one-site fit. All experiments were performed at least in triplicate.

Test B

Receptor Binding Assay using Porcine Myometrial Membrane AT_2 Receptor

Myometrial membranes were prepared from porcine uteri according to the method by Nielsen *et al* (*Clin. Exp. Pharm. Phys.* (1997) **24**, 309). Any possible interference that may be exhibited by binding of compound to AT_1 receptors was blocked by addition of 1 μM of a selective AT1 inhibitor. Binding of [^{125}I]Ang II to membranes was conducted in a final volume of 0.5 mL containing 50 mM Tris-HCl (pH 7.4), 100 mM NaCl, 10 mM $MgCl_2$, 1 mM EDTA, 0.025% bacitracin, 0.2% BSA, homogenate corresponding to 10 mg of the original tissue weight, [^{125}I]Ang II (70 000 cpm, 0.03 nM) and variable concentrations of test substance. Samples were incubated at 25°C for 1 h, and binding was terminated by filtration through Whatman GF/B glass-fiber filter sheets using a Brandel cell harvester. The filters were washed with 3 × 3 mL of Tris-HCl (pH 7.4) and transferred to tubes. The radioactivity was measured using a gamma counter. The characteristics of the Ang II binding AT_2 receptor was determined by using six different concentrations (0.03-5 nmol/L) of the labeled [^{125}I]Ang II.

Non-specific binding was determined in the presence of 1 μM Ang II. The specific binding was determined by subtracting the non-specific binding from the total bound [^{125}I]Ang II. The dissociation constant (K_d = 0.7 ± 0.1 nM, [L] = 0.057 nM) was determined by Scatchard analysis of data obtained with Ang II by using GraFit (Erithacus Software, UK). The binding data were best fitted with a one-site fit. All experiments were performed at least in triplicate .

Test C

Duodenal Mucosal Alkaline Secretion Assay

Compounds were exposed to the duodenal mucosa in barbiturate-anaesthetised rats prepared for *in situ* titration of duodenal mucosal alkaline secretion, according to the methodology described by Flemström *et al* in *Am. J. Physiol.* (1982) **243**, G348.

The invention is illustrated by way of the following examples.

Example 1

N-Butyloxycarbonyl-5-*iso*-butyl-3-(4-tetrazol-2-ylmethylphenyl)-thiophene-2-sulfonamide

(a) *N-tert*-Butylthiophene-2-sulfonamide

Thiophene-2-sulfonyl chloride (15 g, 0.082 mol) was dissolved in $CHCl_3$ (200 mL) under N_2 atmosphere and then cooled to 0°C. *tert*-Butylamine (25.9 mL, 0.246 mol) dissolved in $CHCl_3$ (50 mL) was then added dropwise to the reaction mixture. The reaction mixture was stirred for 1 h at room temperature and then at reflux for 10 min. Toluene (700 mL) was added and the organic phase was washed with water (3 x 50 mL), dried, and concentrated *in vacuo*. The sub-title product was used without further purification in the next step.

^{1}H NMR δ($CDCl_3$): 7.60(1H, dd, J=1.3, 3.8 Hz), 7.53(1H, dd, J=1.3, 5.0 Hz), 7.02(1H, dd, J=5.0, 3.8 Hz), 5.13(1H, m), 1.24 (9H, m)

^{13}C NMR δ($CDCl_3$): 145.0, 131.7, 131.2, 127.0, 55.1, 29.9

(b) 5-*iso*-Butyl-*N*-*tert*-butylthiophene-2-sulfonamide

N-*tert*-Butylthiophene-2-sulfonamide (10 g, 0.046 mol, see step (a) above) was dissolved in THF (85 mL) under N_2 and then cooled to –78°C. *n*-BuLi (1.6 M, 76.9 mL, 0.12 mol) was added *via* a syringe. The reaction mixture was stirred at –78°C for 30 min. and then at –40°C for 2 h. Iodo-2-methylpropane (10.5 mL, 0.09 mol) was added dropwise to the reaction mixture. The reaction mixture was stirred overnight at room temperature. The reaction was quenched with NH_4Cl (aq.) and extracted with EtOAc. The combined organic phase was washed with brine and dried and concentrated *in vacuo*. The crude product was purified on column chromatography (hexanes:EtOAc (10:1)) to give the sub-title compound in 55% yield (7.0 g, 0.025 mol).

^{1}H NMR δ($CDCl_3$): 7.43(1H, d, J= 3.6 Hz), 6.67(1H, d, J=3.8 Hz), 4.83(1H, m), 2.67(2H, d, J=7 Hz), 1.88 (1H, m), 1.26(9H, m), 0.93(6H, J=6.6 Hz).

^{13}C NMR δ($CDCl_3$): 145.0, 131.7, 131.2, 127.0, 55.1, 29.9

(c) 5-*iso*-Butyl-2-(N-*tert*-butylaminosulfonyl)thiophene-3-boronic acid

5-*iso*-Butyl-*N*-*tert*-butylthiophene-2-sulfonamide (10.6 g, 0.039 mol, see step (b) above) was dissolved in THF (165 mL) under N_2 and then cooled to –78°C. *n*-BuLi (1.6 M, 60.19 mL, 0.096 mol) was added *via* a syringe. The reaction mixture was stirred at –20°C for 4 h. The tri-*iso*-propylborate (13.3 mL, 0.058 mol) was then added *via* a syringe and the reaction mixture was stirred overnight at room temperature. The reaction was quenched with 2 M HCl (20 mL). The organic phase was separated and the water phase was extracted with EtOAc (3 x 100 mL). The combined organic phase was

washed with brine, dried and concentrated *in vacuo*. The product was used without further purification.

MS(ESI$^+$) m/z: 236.8

(d) 3-(4-Hydroxymethylphenyl)-5-*iso*-butyl-*N*-*tert*-butylthiophene-2-sulfonamide

5-*iso*-Butyl-2-(N-*tert*-butylaminosulfonyl)thiophene-3-boronic acid (319.3 mg, 1.00 mmol, see step (c) above), 4-bromobenzyl alcohol (374.1 mg, 2.00 mmol), toluene (20 mL), ethanol (4 mL), NaOH (1.0M, 4 mL, 4 mmol) and $Pd(PPh_3)_4$ (34 mg, 0.030mmol) were mixed together under N_2. The mixture was warmed to reflux for 2 hours and was then diluted with EtOAc (50 mL), washed with water and brine and dried over $MgSO_4$. The solvent was removed and the residue was separated by column chromatography using $CHCl_3$:MeOH (40:1) as eluent to give 289 mg of the sub-title compound (yield: 76%).

IR(pure): 3465, 3162, 2952, 2867, 1441 cm^{-1}

^{1}H NMR δ(CD_3OD): 7.59(2H, d, J= 8.2 Hz), 7.45(2H, d, J= 8.2 Hz), 6.75(1H, s), 4.75(2H, s), 4.11(1H, brs), 2.69(2H, d, J= 7.1 Hz), 1.92(1H, m), 0.99(6H, d, J=7.2 Hz), 0.98(9H, s)

^{13}C NMR δ(CD_3OD): 148.3, 142.9, 141.1, 134.2, 130.3, 128.9, 127.6, 126.8, 64.8, 54.5, 39.2, 30.5, 29.5, 22.1

MS(EI$^+$) m/z: 382.0

Anal. Calcd for $C_{19}H_{27}NO_3S_2$: C, 59.8; H, 7.3; N, 3.7. Found: C, 59.6; H, 7.0; N, 3.5

(e) 3-(4-Bromomethylphenyl)-5-*iso*-butyl-*N*-*tert*-butylthiophene-2-sulfonamide

3-(4-Hydroxymethylphenyl)-5-*iso*-butyl-*N*-*tert*-butylthiophene-2-sulfonamide (280 mg, 0.734 mmol, see step (d) above) was dissolved in DMF (10 mL). PPh_3 (459.2 mg, 1.75 mmol) and CBr_4 (580.3, 1.75 mmol) were

added to the resultant solution. The mixture was stirred for 24 h at room temperature and then diluted with ethyl acetate. The organic phase was washed with water (50 mL) and brine (50 mL) and then dried over $MgSO_4$. After removing the solvents, the residue was purified by column chromatography using hexane:acetone (5:1) as eluent to give the sub-title compound (314.9 mg, 0.709 mmol, 76% yield).

IR(pure): 3302, 2952, 2866, 1442 cm^{-1}

^1H NMR $\delta(CDCl_3)$: 7.62(2H, d, J= 8.4 Hz), 7.48(2H, d, J= 8.4 Hz), 6.75(1H, s), 4.56(2H, s), 4.11(1H, brs), 2.69(2H, d, J= 7.1 Hz), 1.92(1H, m), 0.99(6H, d, J=7.2 Hz), 0.98(9H, s)

^{13}C NMR $\delta(CDCl_3)$: 148.5, 142.4, 138.2, 136.9, 135.1, 129.5, 129.1, 128.7, 54.6, 39.2, 32.8, 30.5, 29.5, 22.1

MS(EI^+) m/z: 445.8

(f) 5-*iso*-Butyl-*N*-*tert*-butyl-3-(4-tetrazol-2-ylmethylphenyl)-thiophene-2-sulfonamide

KOH (112.2 mg, 2.00 mmol, crushed pellets) was added to DMSO (10 mL, dried over 4A molecular sieve) and stirred for 5 min. Tetrazole (28.0 mg, 0.4 mmol) was added to the mixture, which was then stirred for 2 h. 3-(4-Bromomethylphenyl)-5-*iso*-butyl-*N*-*tert*-butylthiophene-2-sulfonamide (130 mg, 0.292 mmol, see step (e) above) was added, the mixture was cooled briefly and stirred for an additional hour before water (50 mL) was added. The reaction mixture was extracted with ethyl acetate (250 mL) and the extract was washed with water (2 x 50 mL) and brine (50 mL). The organic phase was dried over $MgSO_4$ and the solvent was removed *in vacuo*. The residue was purified on column chromatography using hexane:acetone (3:1) as eluent to give the sub-title compound (28.6 mg, 0.066 mmol, 23% yield).

IR(pure): 3328, 3134, 2980, 1501, 1466 cm^{-1}

^{1}H NMR δ($CDCl_3$): 8.52(1H, s), 7.64(2H, d, J= 8.3 Hz), 7.46(2H, d, J= 8.3 Hz), 6.73(1H, s), 5.85(2H, s), 2.69(2H, d, J= 7.1 Hz), 1.91(1H, m), 1.58(1H, s), 0.98(15H, brs)

^{13}C NMR δ($CDCl_3$): 153.2, 148.5, 142.4, 136.8, 135.8, 133.2, 129.7, 128.8, 128.5, 56.3, 54.6, 39.2, 30.5, 29.5, 22.1

MS(EI^+) m/z: 434.0

Anal. Calcd for $C_{20}H_{27}N_5O_2S_2 \times H_2O$: C, 53.2; H, 6.5; N, 15.5. Found: C, 53.7; H, 6.1; N, 15.2

(g) 5-*iso*-Butyl-3-(4-tetrazol-2-ylmethylphenyl)thiophene-2-sulfonamide

To a solution of 5-*iso*-butyl-*N*-*tert*-butyl-3-(4-tetrazol-2-ylmethylphenyl)-thiophene-2-sulfonamide (42.1 mg, 0.111 mmol, see step (f) above) in CH_2Cl_2 (10 mL) was added BCl_3 (0.5 mL, 1M, 0.5 mmol) under N_2 (g). The reaction mixture was stirred for 0.5 h. Water (50 mL) was added and the mixture was extracted with ethyl acetate (3 x 50 mL). The combined organic phases were washed with brine and dried over $MgSO_4$ and the solvent was removed *in vacuo*. The crude product was used directly in the next step without further purification.

(h) *N*-Butyloxycarbonyl-5-*iso*-butyl-3-(4-tetrazol-2-ylmethylphenyl)thio-phene-2-sulfonamide

The crude product from step (g) above was dissolved in pyridine (1 mL, dried over 4Å molecular sieve). Pyrrolidinopyridine (14 mg, 0.0095 mmol) and butyl chloroformate (120 µL, 0.97 mmol) were added to the mixture, which was then stirred for 30 hours under N_2(g) at room temperature. The solvent was removed *in vacuo* and then co-evaporated with acetonitrile. Purification using column chromatography with $CHCl_3$:MeOH (35:1) as eluent yielded the title compound (24.9 mg, 0.052 mmol) in 54% yield (from 5-*iso*-butyl-*N*-*tert*-butyl-3-(4-tetrazol-2-ylmethylphenyl)thiophene-2-sulfonamide).

IR(pure): 3330, 2961, 2875, 1743, 1466 cm^{-1}

^1H NMR $\delta(CDCl_3)$: 8.49(1H, s), 7.68(1H, s), 7.48(2H, d, J= 8.2 Hz), 7.40(2H, d, J=8.2 Hz), 6.73(1H, s), 5.82(2H, s), 4.07(2H, t, J= 6.6 Hz), 2.70(2H, d, J= 7.1 Hz), 1.91(1H, m), 1.50(2H, m), 1.24(2H, m), 0.98(6H, d, J= 6.9 Hz), 0.87(3H, J= 7.4 Hz)

^{13}C NMR $\delta(CDCl_3)$: 153.2, 151.8, 150.1, 145.6, 134.8, 133.4, 129.6, 129.3, 128.3, 66.9, 56.3, 39.2, 30.5, 30.4, 22.2, 18.7, 13.6

MS(EI^+) m/z: 478.0

Anal. Calcd for $C_{21}H_{27}N_5O_4S_2$: C, 52.8; H, 5.7; N, 14.7. Found: C, 53.0; H, 5.8; N, 14.1

Example 2

N-Butyloxycarbonyl-5-*iso*-butyl-3-(4-tetrazol-1-ylmethylphenyl)thiophene-2-sulfonamide

(a) 1-(4-Bromobenzyl)-1*H*-tetrazole

Dimethyl sulphoxide (10 mL, dried over 4A molecular sieve) was added to potassium hydroxide (1.12 g, 0.02 mol, crushed pellets) and the mixture was stirred for 5 minutes. 1*H*-Tetrazole (0.35 g, 0.005 mol) was then added and the mixture was stirred for 2 hours. 4-Bromobenzyl bromide (1.87 g, 0.0075 mol) was added and the mixture was cooled briefly and stirred for a further hour before adding water (50 mL). The mixture was extracted with ether (3 × 80 mL) and each extract was washed with water (3 × 50 mL). The combined ether layers were dried over $MgSO_4$ and the solvent using removed *in vacuo*. The residue was chromatographed on silica gel with $CHCl_3$:MeOH (40:1) as eluent yielding the sub-title compound (0.98 g, yield: 82%).

^1H NMR $\delta(CDCl_3)$: 8.64(1H, s), 7.50(2H, d, J= 8.4 Hz), 7.18(2H, d, J= 8.4), 5.56(2H, s)

^{13}C NMR $\delta(CDCl_3)$: 142.4, 132.4, 131.8, 129.9, 123.4, 51.3

MS(ESI$^+$) m/z: 238.8

Anal. Calcd. for $C_8H_7BrN_4$: C, 40.2; H, 3.0; N, 23.4. Found: C, 40.3; H, 3.0; N, 23.4

(b) 5-*iso*-Butyl-*N*-*tert*-butyl-3-(4-tetrazol-1-ylmethylphenyl)thiophene-2-sulfonamide

5-*iso*-Butyl-2-(N-*tert*-butylaminosulfonyl)thiophene-3-boronic acid (401.0 mg, 1.256 mmol, see Example 1(c) above), 1-(4-bromobenzyl)-1*H*-tetrazole (199.4 mg, 0.834 mmol, see step (a) above), toluene (20 mL), ethanol (3.0 mL), NaOH (1.0M, 5.0 mL, 5.0 mmol) and $Pd(PPh_3)_4$ (29.0 mg, 0.25 mmol) were mixed under N_2. The mixture was warmed to reflux for 2 hours. The mixture was diluted with EtOAc (20 mL), washed with water and brine, and dried over $MgSO_4$. The solvent was removed and the residue was separated by column chromatography using $CHCl_3$:MeOH (40:1) as eluent to give 222.4 mg of the sub-title compound (yield: 62%).

IR(pure): 3284, 3134, 2958, 2870, 1513, 1436 cm^{-1}

^{1}H NMR δ($CDCl_3$): 8.71(1H, s), 7.64(2H, d, J= 8.3 Hz), 7.40(2H, d, J= 8.3 Hz), 6.74(1H, s), 5.65(2H, s), 2.67(2H, d, J= 7.1 Hz), 1.94(1H, m), 0.99(15H, m)

^{13}C NMR δ($CDCl_3$): 148.5, 142.6, 142.2, 136.8, 135.9, 133.1, 129.9, 128.8, 128.3, 54.6, 51.7, 39.2, 30.5, 29.5, 22.1

MS(ESI$^+$) m/z: 433

(c) 5-*iso*-Butyl-3-(4-tetrazol-1-ylmethylphenyl)thiophene-2-sulfonamide

BCl_3 (1.0 mL, 1M, 1.0 mmol) was added to a solution of 5-*iso*-butyl-*N*-*tert*-butyl-3-(4-tetrazol-1-ylmethylphenyl)thiophene-2-sulfonamide (177.0 mg, 0.408 mmol, see step (b) above) in CH_2Cl_2 (10 mL) under N_2 (g), and the reaction mixture was stirred for 0.5 h. Water (50 mL) was added and the mixture was extracted with ethyl acetate (3 x 50 mL). The combined organic phases were washed with brine, dried over $MgSO_4$ and the solvent

was removed *in vacuo*. The crude product was used directly in the next step used without further purification.

(d) *N*-Butyloxycarbonyl-5-*iso*-butyl-3-(4-tetrazol-1-ylmethylphenyl)thiophene-2-sulfonamide

The title compound was prepared (89.6 mg, 0.188 mmol, 46% yield (from 5-*iso*-butyl-*N*-*tert*-butyl-3-(4-tetrazol-1-ylmethylphenyl)thiophene-2-sulfonamide)) analogously to the procedure described in Example 1(h) above from the crude 5-*iso*-butyl-3-(4-tetrazol-1-ylmethylphenyl)-thiophene-2-sulfonamide from step (c) above.

IR(pure): 3135, 2959, 2875, 1747, 1464 cm^{-1}

^1H NMR $\delta(CDCl_3)$: 8.73(1H, s), 7.43(2H, d, J= 7.7 Hz), 7.24(2H, d, J= 7.7 Hz), 6.72(1H, s), 5.59(2H, s), 4.00(2H, brs), 2.69(2H, brs), 1.91(1H, m), 1.46(2H, m), 1.19(2H, m), 0.95(6H, d, J= 6.9 Hz), 0.83(3H, J= 6.8 Hz)

^{13}C NMR $\delta(CDCl_3)$: 151.8, 151.4, 145.3, 143.0, 134.8, 133.5, 129.6, 129.1, 127.8, 66.9, 51.4, 39.2, 30.9, 30.4, 22.2, 18.7, 13.6

MS(EI^+) m/z: 478.0

Anal. Calcd for $C_{21}H_{27}N_5O_4S_2 \times \frac{1}{2} H_2O$: C, 51.8; H, 5.8; N, 14.4. Found: C, 51.4; H, 5.6; N, 14.1

Example 3

N-Butyloxycarbonyl-3-(4-[1,2,4]triazol-1-ylmethylphenyl)-5-*iso*-butyl-thiophene-2-sulfonamide

(a) 1-(4-Bromo-benzyl)-1*H*-[1,2,4]triazole

DMF and KOH (3.3 g, 58 mmol) were stirred together at rt for 5 minutes before adding 1,2,4-triazole (1 g, 14.5 mmol). After a further 30 minutes, the reaction mixture was cooled to 0°C and 1-bromo-4-bromomethyl-benzene (7.2 g, 29 mmol) was added dropwise over 5 minutes. The reaction mixture was heated to 60°C, then cooled to rt, extracted with ethyl acetate

and water, and subsequently dried over K_2CO_3. The solvent was evaporated to yield yellow-white crystals, which, upon repeated recrystallisation, (ethylacetate/isohexane) yielded 0.60 g of the sub-title compound as white crystals (62% isolated yield).

^{1}H NMR δ(270 MHz, $CDCl_3$): 8.11 (s, 1H), 7.96 (s, 1H), 7.51-7.38 (m, 2H), 7.15-7.10 (m, 2H), 5.29 (s, 2H)

^{13}C NMR δ(67.8 MHz, $CDCl_3$): 152.2, 143.0, 133.5, 132.1, 129.5, 122.7, 52.8

MS m/z 238 ($M^+ + 1$)

(b) 3-(4-[1,2,4]Triazol-1-ylmethylphenyl)-5-*iso*-butyl-*N*-*tert*-butylthiophene-2-sulfonamide

5-*iso*-Butyl-2-(N-*tert*-butylaminosulfonyl)thiophene-3-boronic acid (0.479 g, 1.5 mmol, see Example 1(c) above), 1-(4-bromobenzyl)-1*H*-[1,2,4]triazole (0.238 g, 1 mmol, see step (a) above), $Pd(OAc)_2$ (15.7 mg, 0.03 mmol), triphenyl phosphine (15.7 mg, 0.06 mmol) and NaOH (0.16 g, 4 mmol) were dissolved in 4 mL of toluene/ethanol (4:1) in a thick walled glass tube, and were then heated to 80°C for 1 h. The reaction mixture was cooled to rt, extracted with ethyl acetate and water and subsequently dried over K_2CO_3. The solvent was evaporated and the reaction mixture was separated on a silica column (dichloromethane + 1% methanol to dichloromethane + 4% methanol) to yield 0.288 g of the sub-title compound (65% yield).

^{1}H NMR δ(270 MHz, $CDCl_3$): 8.13 (s, 1H), 7.94 (s, 1H), 7.60-7.57 (m, 2H), 7.33-7.30 (m, 2H), 6.72 (s, 1H), 5.37 (s, 2H), 4.47 (s, 1H), 2.65, (d, J = 7 Hz, 2H), 1.89 (sept J = 7 Hz, 1H), 0.96 (s, 9H), 0.94 (d, J = 7 Hz, 6H)

^{13}C NMR δ(67.8 MHz, $CDCl_3$): 152.1, 148.5, 143.1, 142.3, 136.6, 135.2, 134.8, 129.6, 128.8, 128.0, 54.5, 53.1, 39.1, 30.4, 29.4, 22.1

MS m/z 433 ($M^+ + 1$)

(c) 3-(4-[1,2,4]Triazol-1-ylmethylphenyl)-5-*iso*-butylthiophene-2-sulfonamide

3-(4-[1,2,4]Triazol-1-ylmethylphenyl)-5-*iso*-butyl-*N*-*tert*-butylthiophene-2-sulfonamide (146.4 mg, 0.34 mmol, see step (b) above) was mixed with BCl_3 (1M solution in hexane) (2 mL, 1.7 mmol) in 5 mL of dichloromethane at rt and stirred for 1 h. The reaction mixture was extracted with ethyl acetate and water and subsequently dried over K_2CO_3. The solvent was evaporated and the resultant product was sufficiently pure to be used directly in the next step.

(d) *N*-Butyloxycarbonyl-3-(4-[1,2,4]triazol-1-ylmethylphenyl)-5-*iso*-butylthiophene-2-sulfonamide

59 mg (0.16 mmol) of the crude 3-(4-[1,2,4]triazol-1-ylmethylphenyl)-5-*iso*-butylthiophene-2-sulfonamide from step (c) above was mixed with butyl chloroformate (31 μL, 0.24 mmol) and DMAP (2 mg, 16 μmol) in 5 mL of triethylamine at 0°C. The reaction mixture was stirred overnight and then diluted with ethyl acetate, washed with water and dried over K_2CO_3. The reaction mixture was then separated on a silica column (dichloromethane + 15% methanol), circular chromatography (dichloromethane + 10-15% methanol and preparative LC-MS to yield 7.0 mg of the title compound (9 % isolated yield).

^{1}H NMR δ(270 MHz, $CDCl_3$): 8.11 (s, 1H), 7.98 (s, 1H), 7.50-7.47 (m, 2H), 7.29-7.26 (m, 2H), 6.74 (s, 1H), 5.39 (s, 2H), 4.05 (t, J = 7 Hz, 2H), 2.71 (d, J = 7 Hz, 2H), 1.95 (sept, J = 7 Hz, 1H), 1.52 (pent, J = 7 Hz, 2H), 1.26 (sext, J = 7 Hz, 2H), 0.99 (d, J = 7 Hz, 6H), 0.88 (t, J = 7 Hz, 3H)

^{13}C NMR δ(67.8 MHz, $CDCl_3$): 151.9, 151.1, 145.1, 143.4, 134.7, 134.2, 131.6, 129.7, 129.0, 127.8, 66.3, 53.2, 39.2, 30.4, 30.3, 22.1, 18.7, 13.5

MS m/z (relative intensity 30 eV) 477 (M^+ + 1)

Example 4

N-(Butylamino)carbonyl-3-(4-imidazole-1-ylmethylphenyl)-5-*iso*-butyl-thiophene-2-sulfonamide

(a) 1-(4-Bromobenzyl)-1H-imidazole

Dimethyl sulphoxide (20 mL, dried over 4Å molecular sieves) was added to potassium hydroxide (2.24 g, 0.04 mol, crushed pellets) and the mixture was stirred for 5 min. Imidazole (0.5718 g, 0.0084 mol) was then added and the mixture was stirred for 2 hours. 4-Bromobenzyl bromide (3.25 g, 0.013 mol) was added and the mixture was cooled briefly and stirred for a further hour before adding water (20 mL). The mixture was extracted with ether (3 × 100 mL) and each extract was washed with water (3 × 50 mL). The combined ether layers were dried over $CaCl_2$ and the solvent was removed *in vacuo*. The residue was chromatographed on silica gel with $CHCl_3$/MeOH (30:1) plus 0.05% formic acid as eluent yielding the sub-title compound (1.275 g, yield: 53%).

^{1}H NMR δ($CDCl_3$): 7.73 (m, 3H), 7.28 (m, 3H), 7.15 (m, 1H), 5.30 (s, 2H)

^{13}C NMR δ($CDCl_3$): 136.8, 134.8, 131.5, 129.3, 128.4, 121.5, 118.7, 49.4

MS (ESI^+) *m/z*: 236.8

(b) 3-(4-Imidazol-1-ylmethylphenyl)-5-*iso*-butyl-N-*tert*-butylthiophene-2-sulfonamide

5-*iso*-Butyl-2-(*N*-*tert*-butylaminosulfonyl)thiophene-3-boronic acid (200.5 mg, 0.628 mmol, see Example 1(c) above), 1-(4-bromobenzyl)-1H-imidazole (98.8 mg, 0.416 mmol, see step (a) above), toluene (15 mL), ethanol (15 mL), NaOH (1.0M, 1.5 mL, 1.5 mmol) and $Pd(PPh_3)_4$ (14.5 mg, 0.125 mmol) were mixed under N_2. The mixture was warmed to reflux for 2 hours. The mixture was diluted with EtOAc (50 mL), washed with water and brine, and dried over $MgSO_4$. The solvent was removed and the residue

was separated by column chromatography with chloroform:methanol (20:1) as eluent to give 113.9 mg of the sub-title compound (yield: 63.27%).

IR (neat, cm^{-1}) ν 3060, 2996, 1507

^1H NMR δ($CDCl_3$): 7.39 (s, 1H), 7.35 (d, J = 8.1 Hz, 2H), 6.98 (d, J = 8.1 Hz, 2H), 6.96 (s, 1H), 6.84 (s, 1H), 6.47 (s, 1H), 4.91 (s, 2H), 3.96 (s, 1H), 2.72 (brs, 1H), 2.42 (d, J = 7.1 Hz, 2H), 1.64 (m, 1H), 0.73 (s, 9H), 0.72 (d, J = 6.9 Hz, 6H)

^{13}C NMR δ($CDCl_3$): 148.6, 142.3, 137.2, 136.2, 135.1, 129.7, 129.4, 128.8, 127.4, 119.2, 54.6, 50.6, 39.2, 30.5, 29.5, 22.1

MS (ESI^+) *m/z*: 431.9

Anal. Calcd for $C_{22}H_{29}N_3O_2S_2$: C, 58.8; H, 7.0; N, 9.4. Found: C, 58.7.0; H, 6.7; N, 9.1

(c) 3-(4-Imidazol-1-ylmethylphenyl)-5-*iso*-butylthiophene-2-sulfonamide

To a solution of 3-(4-imidazol-1-ylmethylphenyl)-5-*iso*-butyl-N-*tert*-butylthiophene-2-sulfonamide (0.097 mmol, 42.0 mg, see step (b) above) in CH_2Cl_2 (10 mL) was added BCl_3 (0.5 mL, 1M, 0.5 mmol) under N_2 (g). The mixture was stirred for 0.5 h. Water (50 mL) was added and the mixture was extracted with ethyl acetate (3 x 50 mL). The combined organic phases were washed with brine and dried over $MgSO_4$ and the solvent was removed *in vacuo*. The crude product was used directly in the next step without further purification.

(d) *N*-(Butylamino)carbonyl-3-(4-imidazole-1-ylmethylphenyl)-5-*iso*-butyl-thiophene-2-sulfonamide

The crude product from step (c) above was dissolved in acetone (5 mL) under N_2 (g). NaOH (0.20 mL, 1M, 0.20 mmol) was added to the mixture, which was then stirred for 10 min. Butyl isocyanate (109 μL, 0.97 mmol) was then added and the mixture was stirred overnight at room temperature. The reaction mixture was then diluted with ethyl acetate (150 mL) and

washed with water and brine. The organic phase was dried over $MgSO_4$ and the solvent was removed *in vacuo*. Purification using column chromatography with $CHCl_3$:MeOH (10:1) as eluent yielded the title compound (15.1 mg, 0.032 mmol) in 33% yield (from 3-(4-imidazol-1-ylmethylphenyl)-5-*iso*-butylthiophene-2-sulfonic acid *tert*-butylamide).

IR (neat, cm^{-1}) ν 3261, 3120, 2957, 2869, 1701, 1514

^1H NMR δ($CDCl_3$, CH_3OD): 7.64 (s, 1H), 7.49 (d, J = 8.1 Hz, 2H), 7.11 (d, J = 8.1 Hz, 2H), 6.97 (brs 1H), 6.90 (brs, 1), 6.72 (s, 1H), 6.24 (brs, 1H), 5.10 (s, 2H), 3.08 (m, 2H), 2.62 (d, J = 7.1 Hz, 2H), 1.92 (m, 1H), 1.20 (m, 4H), 0.99 (d, J = 6.6, 6H), 0.86 (t, J = 7.1 Hz, 3H)

^{13}C NMR δ($CDCl_3$, CH_3OD): 152.2, 150.0, 144.5, 137.0, 135.9, 134.4, 133.0, 129.7, 129.5, 128.1, 127.1, 119.5, 50.7, 39.9, 39.2, 31.6, 30.5, 22.2, 19.8, 13.7

MS (ESI^+) *m/z*: 475.2

Example 5

N-Butylsulfonyl-3-(4-imidazole-1-ylmethylphenyl)-5-*iso*-butylthiophene-2-sulfonamide

Crude 3-(4-imidazol-1-ylmethylphenyl)-5-*iso*-butylthiophene-2-sulfonamide (prepared according to the procedure described in Example 4(c) above) was dissolved in THF (3 mL) under N_2 (g). NaOH (1.0 mL, 1M, 1.0 mmol) was added to the mixture, which was then stirred for 10 min. Butanesulfonyl chloride (45 μL, 0.35 mmol) was then added, and the mixture was stirred for 24 h at room temperature. The reaction mixture was then diluted with ethyl acetate (150 mL) and washed with water and brine. The organic phase was dried over $MgSO_4$ and the solvent was removed *in vacuo*. The crude product was recrystallised from acetone to yield the title compound (31.7 mg, 0.064 mmol).

IR (neat, cm^{-1}) ν 3133, 2959, 2871, 1576, 1543, 1514

^{1}H NMR δ($CDCl_3$, CH_3OD): 8.70 (s, 1H), 7.64 (d, J = 8.1 Hz, 2H), 7.08-7.20 (m, 5H), 6.59 (s, 1H), 5.06 (s, 2H), 3.08 (m, 2H), 2.57 (d, J = 7.1 Hz, 2H), 1.67 (m, 1H), 1.65 (m, 2H), 1.29 (m, 2H), 0.89-0.79 (m, 9H)

^{13}C NMR δ($CDCl_3$, CH_3OD): 146.8, 140.9, 138.2, 136.8, 135.0, 131.9, 130.4, 128.6, 127.9, 121.2, 119.8, 54.0, 52.5, 38.9, 30.3, 25.6, 21.9, 21.4, 13.4

MS (ESI^+) *m/z*: 496.1

Example 6

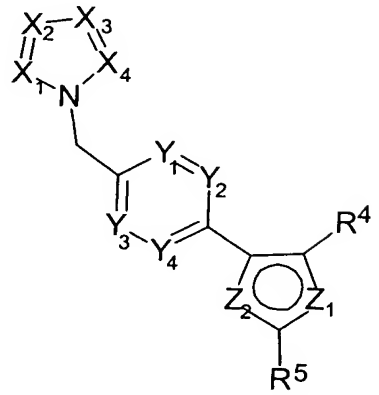
Title compounds of the Examples were tested in Tests A and B above and were found to exhibit an affinity for AT2 receptors of less than Ki = 100 nM (e.g. less than 50 nM) and an affinity to AT1 receptors of more than Ki = 1 μM.

Example 7

Title compounds of the Examples are tested in Test C above and are found to stimulate markedly mucosal alkalisation. This effect is blocked by co-administration of the selective AT2 receptor antagonist PD123319 (Sigma Chemical Company).

Claims

1. A compound of formula I,



I

wherein

one of X_1 and X_2 represents –N- and the other represents $-C(R^1)-$;

X_3 represents –N- or $-C(R^2)-$;

X_4 represents –N- or $-C(R^3)-$;

R^1, R^2 and R^3 independently represent H, C_{1-6} alkyl, C_{1-6} alkoxy, C_{1-6} alkoxy-C_{1-6}-alkyl or halo;

provided that, when X_1 represents $-C(R^1)-$, X_3 represents $-C(R^2)-$ and X_4 represents $-C(R^3)-$, then R^1 represents H;

Y_1, Y_2, Y_3 and Y_4 independently represent –CH- or -CF-;

Z_1 represents –CH-, -O-, -S-, -N- or -CH=CH-;

Z_2 represents –CH-, -O-, -S- or –N-;

provided that:

(a) Z_1 and Z_2 are not the same;

(b) when Z_1 represents –CH=CH-, then Z_2 may only represent –CH- or –N-; and

(c) other than in the specific case in which Z_1 represents –CH=CH-, and Z_2 represents –CH-, when one Z_1 and Z_2 represents –CH-, then the other represents –O- or –S-;

R^4 represents $-S(O)_2N(H)C(O)R^6$, $-S(O)_2N(H)S(O)_2R^6$, $-C(O)N(H)S(O)_2R^6$, or, when Z_1 represents –CH=CH-, R^4 may represent $-N(H)S(O)_2N(H)C(O)R^7$ or $-N(H)C(O)N(H)S(O)_2R^7$;

R^5 represents C_{1-6} alkyl, C_{1-6} alkoxy or C_{1-6} alkoxy-C_{1-6}-alkyl;

R^6 represents C_{1-6} alkyl, C_{1-6} alkoxy, C_{1-6} alkoxy-C_{1-6}-alkyl, C_{1-6} alkylamino or di-C_{1-6} alkylamino; and

R^7 represents C_{1-6} alkyl,

or a pharmaceutically-acceptable salt thereof,

provided that, when X_1, X_3 and X_4 all represent –CH-, Y_1, Y_2, Y_3 and Y_4 all represent –CH-, Z_1 represents –S- or –CH=CH-, Z_2 represents –CH- and R^5 represents *n*-butyl or *iso*-butyl, then R^4 does not represent $-S(O)_2N(H)C(O)R^6$, in which R^6 represents -O-*n*-butyl, -O-*iso*-propyl, -O-*iso*-butyl or $-CH_2$-O-*n*-butyl.

2. A compound as claimed in Claim 1 wherein, when X_1 represents $–C(R^1)-$, then X_3 represents $–C(R^2)-$ and X_4 represents –N-.

3. A compound as claimed in Claim 2 wherein R^1 represents H.

4. A compound as claimed in Claim 1 wherein, when X_1 represents $–C(R^1)-$, then X_3 and X_4 both represent N.

5. A compound as claimed in Claim 1 wherein, when X_1 represents $–C(R^1)-$, then X_3 represents $-C(R^2)-$ and X_4 represents $–C(R^3)-$.

6. A compound as claimed in Claim 1, wherein, when X_1 represents –N-, then X_3 represents –N-.

7. A compound as claimed in Claim 6 wherein, when X_4 represents $-C(R^3)-$, then R^3 represents H.

8. A compound as claimed in any one of Claims 1, 2 or 4 to 7, wherein R^1 represents H or C_{1-3} alkyl.

9. A compound as claimed in Claim 8, wherein R^1 represent H or ethyl.

10. A compound as claimed in any one of Claims 1 to 3, 5, 8 or 9 wherein R^2 represents C_{1-3} alkyl, halo or H.

11. A compound as claimed in Claim 10 wherein R^2 represents H.

12. A compound as claimed in any one of Claims 1, 5, 6 or 8 to 10 wherein R^3 represents C_{1-3} alkyl, halo or H.

13. A compound as claimed in Claim 12 wherein R^3 represents H.

14. A compound as claimed in any one of the preceding claims wherein Y_1, Y_2, Y_3 and Y_4 all represent –CH-.

15. A compound as claimed in any one of the preceding claims wherein Z_1 represents -S- or –CH=CH-.

16. A compound as claimed in any one of the preceding claims wherein Z_2 represents –CH-.

17. A compound as claimed in any one of the preceding claims wherein R^4 represents $S(O)_2N(H)C(O)R^6$.

18. A compound as claimed in any one of the preceding claims wherein R^5 represents *n*-butyl or *iso*-butyl.

19. A compound as claimed in any one of the preceding claims wherein, when R^4 represents $-S(O)_2N(H)C(O)R^6$, $-S(O)_2N(H)S(O)_2R^6$ or $-C(O)N(H)S(O)_2R^6$, R^6 represents *n*-butoxymethyl, *iso*-butoxy or *n*-butoxy.

20. A pharmaceutical formulation including a compound as defined in any one of Claims 1 to 19, or a pharmaceutically acceptable salt thereof, in admixture with a pharmaceutically acceptable adjuvant, diluent or carrier.

21. A compound as defined in any one of Claims 1 to 19, or a pharmaceutically acceptable salt thereof, for use as a pharmaceutical.

22. A compound as defined in any one of Claims 1 to 19, or a pharmaceutically acceptable salt thereof, for use in the treatment of a condition in which selective agonism of the AT2 receptor is desired and/or required.

23. A compound as defined in any one of Claims 1 to 19, or a pharmaceutically acceptable salt thereof, for use in the treatment of a condition in which endogenous production of AngII is deficient.

24. A compound as defined in any one of Claims 1 to 19, or a pharmaceutically acceptable salt thereof, for use in the treatment of a condition in which an increase in the effect of AngII is desired or required.

25. A compound as defined in any one of Claims 1 to 19, or a pharmaceutically acceptable salt thereof, for use in the treatment of a

condition where AT2 receptors are expressed and their stimulation is desired or required.

26. The use of a compound as defined in any one of Claims 1 to 19, or a pharmaceutically acceptable salt thereof, for the manufacture of a medicament for the treatment of a condition in which selective agonism of the AT2 receptor is desired and/or required.

27. The use of a compound as defined in any one of Claims 1 to 19, or a pharmaceutically acceptable salt thereof, for the manufacture of a medicament for the treatment of a condition in which endogenous production of AngII is deficient.

28. The use of a compound as defined in any one of Claims 1 to 19, or a pharmaceutically acceptable salt thereof, for the manufacture of a medicament for the treatment of a condition in which an increase in the effect of AngII is desired or required.

29. The use of a compound as defined in any one of Claims 1 to 19, or a pharmaceutically acceptable salt thereof, for the manufacture of a medicament for the treatment of a condition where AT2 receptors are expressed and their stimulation is desired or required.

30. The use as claimed in any one of Claims 26 to 29, wherein the condition is of the gastrointestinal tract, the cardiovascular system, the respiratory tract, the kidneys, the eyes, the female reproductive (ovulation) system, or the central nervous system.

31. The use as claimed in Claim 30, wherein the condition is oesophagitis, a gastric ulcer, a duodenal ulcer, dyspepsia (including non-ulcer dyspepsia),

gastro-oesophageal reflux, irritable bowel syndrome, inflammatory bowel disease, pancreatitis, hepatitis, gall bladder disease, multiple organ failure, sepsis, xerostomia, gastritis, gastroparesis, hyperacidity, a disorder of the bilary tract, coelicia, Crohn's disease, ulcerative colitis, diarrhoea, constipation, colic, dysphagia, vomiting, nausea, indigestion, Sjögren's syndrome, inflammatory disorders, asthma, an obstructive lung disease, pneumonitis, pulmonary hypertension, adult respiratory distress syndrome, renal failure, nephritis, renal hypertension, diabetic retinopathy, premature retinopathy, retinal microvascularisation, ovulatory dysfunction, hypertension, cardiac hypertrophy, cardiac failure, artherosclerosis, arterial thrombosis, venous thrombosis, endothelial dysfunction, endothelial lesions, post baloon dilatation stenosis, angiogenesis, diabetic complications, microvascular dysfunction, cognitive dysfunctions, dysfunctions of food intake (hunger/satiety), thirst, stroke, cerebral bleeding, cerebral embolus, cerebral infarction, hypertrophic disorders, prostate hyperplasia, autoimmune disorders, psoriasis, obesity, neuronal regeneration, an ulcer, adipose tissue hyperplasia, stem cell differentiation and proliferation, cancer, apoptosis, tumours or hypertrophy.

32. The use as claimed in Claim 31, wherein the condition is non-ulcer dyspepsia, irritable bowel syndrome, multiple organ failure, hypertension or cardiac failure.

33. A method of treatment of a condition in which selective agonism of the AT2 receptor is desired and/or required, which method comprises administration of a therapeutically effective amount of a compound as defined in any one of Claims 1 to 19, or a pharmaceutically acceptable salt thereof, to a person suffering from, or susceptible to, such a condition.

34. A pharmaceutical formulation including a compound as defined in any one of Claims 1 to 19, or a pharmaceutically acceptable salt thereof, and an AT1 receptor antagonist, in admixture with a pharmaceutically-acceptable adjuvant, diluent or carrier.

35. A kit of parts comprising components:

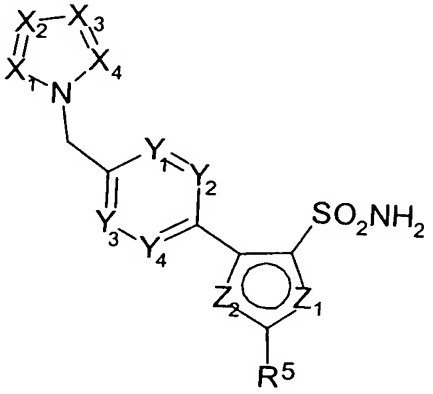
(a) a pharmaceutical formulation including a compound as defined in any one of Claims 1 to 19, or a pharmaceutically acceptable salt thereof, in admixture with a pharmaceutically-acceptable adjuvant, diluent or carrier; and

(b) a pharmaceutical formulation including an AT1 receptor antagonist, in admixture with a pharmaceutically-acceptable adjuvant, diluent or carrier,

which components (a) and (b) are each provided in a form that is suitable for administration in conjunction with the other.

36. A process for the preparation of a compound as defined in Claim 1, which comprises:

(i) for compounds of formula I in which R^4 represents $-S(O)_2N(H)C(O)R^6$ or $-S(O)_2N(H)S(O)_2R^6$, and R^6 is as defined in Claim 1, reaction of a compound of formula II,



II

wherein X_1, X_2, X_3, X_4, Y_1, Y_2, Y_3, Y_4, Z_1, Z_2 and R^5 are as defined in Claim 1 with a compound of formula III,

$$R^6GL^1 \qquad \text{III}$$

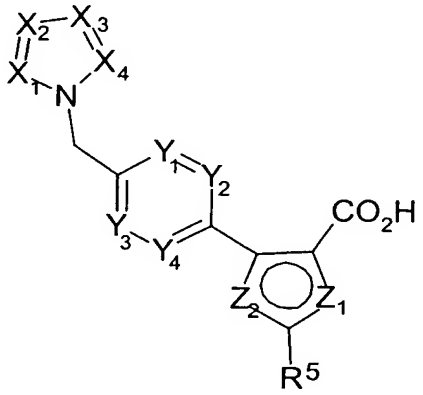
wherein G represents C(O) or $S(O)_2$ (as appropriate), L^1 represents a suitable leaving group and R^6 is as defined in Claim 1;

(ii) for compounds of formula I in which R^4 represents $-S(O)_2N(H)C(O)R^6$ and R^6 represents C_{1-6} alkoxy-C_{1-6}-alkyl, coupling of a compound of formula II as defined above with a compound of formula IV,

$$R^{6a}CO_2H \qquad \text{IV}$$

wherein R^{6a} represents C_{1-6} alkoxy-C_{1-6}-alkyl;

(iii) for compounds of formula I in which R^4 represents $-C(O)N(H)S(O)_2R^6$ and R^6 is as defined in Claim 1, coupling of a compound of formula V,



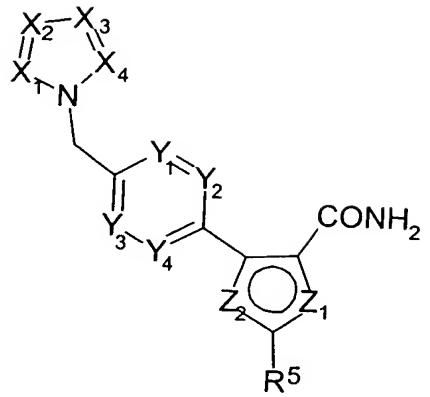
V

wherein X_1, X_2, X_3, X_4, Y_1, Y_2, Y_3, Y_4, Z_1, Z_2 and R^5 are as defined in Claim 1, with a compound of formula VI,

$$R^6S(O)_2NH_2 \qquad \text{VI}$$

wherein R^6 is as defined in Claim 1;

(iv) for compounds of formula I in which R^4 represents $-C(O)N(H)S(O)_2R^6$ and R^6 is as defined in Claim 1, coupling of a compound of formula VA,



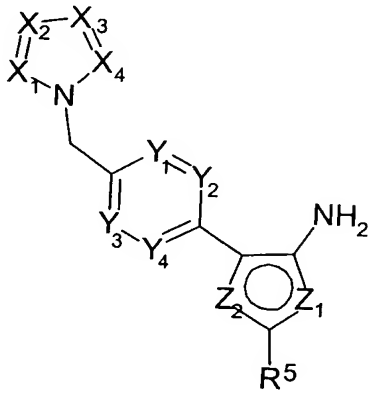
VA

wherein X_1, X_2, X_3, X_4, Y_1, Y_2, Y_3, Y_4, Z_1, Z_2 and R^5 are as defined in Claim 1, with a compound of formula VIA,

$$R^6S(O)_2Cl \qquad \text{VIA}$$

wherein R^6 is as defined in Claim 1;

(v) for compounds of formula I in which R^4 represents $-N(H)S(O)_2N(H)C(O)R^7$ and R^7 is as defined in Claim 1, reaction of a compound of formula VII,



VII

wherein X_1, X_2, X_3, X_4, Y_1, Y_2, Y_3, Y_4, Z_1, Z_2 and R^5 are as defined in Claim 1, with a compound of formula VIII,

$$R^7C(O)N(H)S(O)_2Cl \qquad \text{VIII}$$

wherein R^7 is as defined in Claim 1;

(vi) for compounds of formula I in which R^4 represents $-N(H)C(O)N(H)S(O)_2R^7$ and R^7 is as defined in Claim 1, reaction of a compound of formula VII as defined above with a compound of formula IX,

$$R^7S(O)_2N(H)C(O)OR^x \qquad \text{IX}$$

wherein R^x represents C_{1-2} alkyl and R^7 is as defined in Claim 1;

(vii) for compounds of formula I in which R^4 represents $-N(H)C(O)N(H)S(O)_2R^7$ and R^7 is as defined in Claim 1, reaction of a compound of formula VII as defined above with a compound of formula X,

$$R^7S(O)_2NCO \qquad X$$

wherein R^7 is as defined in Claim 1; or

(viii) for compounds of formula I in which R^4 represents $-S(O)_2N(H)C(O)R^6$ and R^6 represents C_{1-6} alkylamino, reaction of a compound of formula II as defined above with a compound of formula XA,

$$R^{6a}NCO \qquad XA$$

wherein R^{6a} represents C_{1-6} alkyl.

37. A compound of formula II as defined in Claim 36 or a protected derivative thereof.

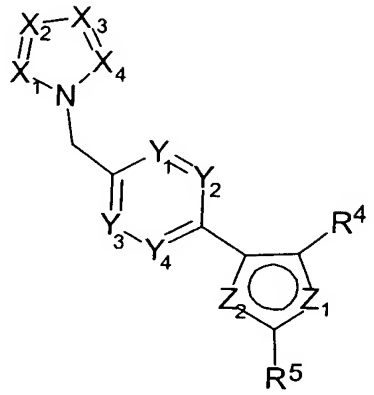
38. A compound of formula V as defined in Claim 36 or a protected derivative thereof.

39. A compound of formula VA as defined in Claim 36 or a protected derivative thereof.

40. A compound of formula VII as defined in Claim 36 or a protected derivative thereof.

ABSTRACT

There is provided a compound of formula I,



I

wherein X_1, X_2, X_3, X_4, Y_1, Y_2, Y_3, Y_4, Z_1, Z_2, R^4 and R^5 have meanings given in the description, and pharmaceutically-acceptable salts thereof, which compounds are useful as selective agonists of the AT2 receptor, and thus, in particular, in the treatment of *inter alia* gastrointestinal conditions, such as dyspepsia, IBS and MOF, and cardiovascular disorders.